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<b>(21) International Application Number:</b> PCT/US93/02684 <b>(22) International Filing Date:</b> 19 March 1993 (19.03.93) <b>(71) Applicant (for all designated States except US):</b> HANDELMAN, Joseph, H. [US/US]; 26 West 61 Street, New York, NY 10023 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> BOXALL, Brian, Alfred [GB/GB]; 51 Chatsworth Avenue, Winnersh, Wokingham, Berkshire RG11 5EU (GB). AMERY, Geoffrey, Wilfred [GB/GB]; 183 Church Road, Earley, Reading, Berkshire RG6 1HN (GB). AHLUWALIA, Gurpreet, S. [US/US]; 8632 Stableview Court, Gaithersburg, MD 20882 (US). <b>(74) Agents:</b> GALLOWAY, Peter, D. et al.; Ladas & Parry, 26 West 61 Street, New York, NY 10023 (US).		<b>(81) Designated States:</b> AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, RO, RU, SD, SE, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).  <b>Published</b> With international search report.
<b>(54) Title:</b> TOPICAL COMPOSITION FOR INHIBITING HAIR GROWTH  <b>(57) Abstract</b>  The present invention embraces a topical composition for inhibiting mammalian hair growth, particularly human beard hair growth (including hirsutism), comprising a water-soluble, hair-growth-inhibiting agent dispersed in an oil-in-water emulsion in the form of a lotion or cream. The invention also embraces a method of inhibiting mammalian hair growth by applying an effective amount of the above composition to the skin. The invention further embraces a topical composition for delivering a pharmacological agent to the skin.		

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TOPICAL COMPOSITION FOR INHIBITING HAIR GROWTHBackground of the Invention

This invention relates to a new topical composition for inhibiting mammalian hair growth. It also relates to a method of inhibiting hair growth by applying a topical composition according to this invention to the skin.

In U.S. 4,720,489 it is disclosed that the topical application of a composition comprising an ornithine decarboxylase ("ODC") inhibitor will inhibit hair growth, including beard hair growth. A particularly advantageous ODC inhibitor for use in this application is 2-(difluoromethyl)-2,5-diaminopentanoic acid, also identified as  $\alpha$ -(difluoromethyl)ornithine ("DFMO"). This patent demonstrates the effectiveness of ODC inhibitors for inhibiting hair growth by measuring changes in flank organ hair mass in adult male hamsters treated with ethanol solutions of such compounds. The patent also generally proposes the possible incorporation of ODC inhibitors in cosmetic formulations such as skin lotions and creams, but the effectiveness of such proposed formulations and their stability and aesthetic attributes are unknown. Since DFMO is a highly

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ionic material, it would tend to destabilize emulsion systems and would be difficult to formulate in such systems, particularly at higher dosage levels necessary to achieve maximum efficacy.

In U.S. 5,095,007, U.S. 5,096,911, and U.S. 5,132,293, additional hair growth inhibitors are disclosed which are completely unrelated to the aforementioned ODC inhibitors. However, each of these patents discloses a water-ethanol vehicle for delivering the active compound. The vehicle comprises 68% water, 16% ethanol, 5% propylene glycol, 5% dipropylene glycol, 4% benzyl alcohol, and 2% propylene carbonate. This vehicle is not aesthetically pleasing or easy to use since it is very runny and feels wet and tacky. Moreover, the efficacy of the active material in this vehicle may not be optimum even though the vehicle contains two known penetration enhancers, namely benzyl alcohol and propylene carbonate.

It is an object of the present invention to provide a topical composition for inhibiting hair growth which is stable, highly efficacious and aesthetically pleasing.

#### Summary of the Invention

The present invention embraces a topical composition for inhibiting mammalian hair growth, particularly human beard hair growth (including hirsutism), comprising a water-soluble, hair-growth-inhibiting agent dispersed in an oil-in-water emulsion in the form of a lotion or cream. The invention also embraces a method of inhibiting mammalian hair growth by applying an effective amount of the above composition to the skin. The invention further embraces a topical composition for

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delivering a water-soluble, pharmacological agent to the skin.

Detailed Description of the Invention

5       The hair growth inhibiting agent which  
is utilized in the composition and method of the  
present invention may be any water-soluble,  
hair-growth-inhibiting agent, particularly any  
highly ionic, water-soluble, hair-growth-  
inhibiting agent. Such active agents may be  
10   selected from any of the classes of agents  
described in the aforementioned U.S. patents,  
namely U.S. 4,720,489, U.S. 5,095,007, U.S.  
5,096,911, and U.S. 5,132,293, provided such  
agents are water soluble. In a preferred  
15   embodiment, the hair growth inhibiting agent is  
2-(difluoromethyl-2,5-diaminopentanoic acid,  
which is also identified as  
 $\alpha$ -(difluoromethyl)ornithine, hereinafter  
abbreviated "DFMO".

20       The topical composition of the present  
invention comprises about 1 to 20 parts by  
weight, preferably 5 to 15 parts, of the  
aforescribed water-soluble, hair-growth-  
inhibiting agent, particularly DFMO, dispersed  
25   in 99 to 80 parts by weight, preferably 95 to 85  
parts, of a vehicle comprising an oil-in-water  
emulsion of the formula (the last two  
ingredients being optional):

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	<u>Ingredient</u>	<u>Wt. Percent</u>	<u>Ex. I</u>	<u>Ex. II</u>
	Water	78 to 87	80.84*	85.53*
	Glyceryl Stearate SE <sup>1</sup>	2.8 to 4.8	4.24	2.97
	PEG-100 Stearate <sup>1</sup>	2.7 to 4.7	4.09	2.86
5	Cetearyl Alcohol <sup>2</sup>	1.9 to 3.3	3.05	2.14
	Ceteareth-20 <sup>2</sup>	1.6 to 2.7	2.50	1.75
	Mineral Oil	1.7 to 2.7	2.22	2.22
	Stearyl Alcohol <sup>3</sup>	1.0 to 2.0	1.67	1.17
	Dimethicone <sup>4</sup>	0.3 to 1.0	0.56	0.56

10

	Citric Acid <sup>5</sup>	0 to 0.5	-	0.25
	Sodium Hydroxide <sup>6</sup>	q.s.	q.s.	q.s.

\* 0.5% water withheld for subsequent pH adjustment.

- 15    1    Available as a blend, for example Cithrol  
GMS A/S ES0743 from Croda Chemicals Ltd.  
(U.K.).
- 2    Available as a blend, for example Cosmowax  
EM5483 from Croda Chemicals Ltd. (U.K.).
- 20    3    Available as Lorol-18 from Henkel Chemicals  
Ltd.
- 4    Available as Silicone Fluid 200 - 100 cps  
from Dow Corning Corporation (e.g., 360  
Medical Fluid or Q7-9120 Fluid).
- 25    5    Other weak acids may be substituted, for  
example lactic, tartaric or phosphoric  
acids to serve as a pH buffer.
- 6    Quantity sufficient to adjust pH to about  
3.5. Other strong bases, such as KOH, may  
30    be used or, in some cases, strong acids  
such as HCl, where the pH needs to be  
lowered.

35    The active agent plus vehicle will  
total 100 parts by weight when finished. Minor  
amounts of other ingredients, such as dyes,  
fragrances, and biocidal agents or preservatives  
may be incorporated in the vehicle as deemed

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necessary or desirable. It is preferred to add about 0.5 to 0.9 parts of Phenonip, a biocidal agent available from Nipa Laboratories Ltd. (U.K.), to the above formulation.

5           The following procedure is carried out to make the vehicle utilized in the topical composition of the present invention. The water and water soluble components, are charged to a mixing vessel, the pH is adjusted to about 3.5,  
10           and the solution is heated to about 70°C. The oil soluble components, except for the biocidal agent, are melted together at about 70°C., then run into the water phase with brisk stirring. Mixing is continued for about twenty minutes,  
15           then water cooling is applied. The biocidal agent is added at 40-45°C. and stirring is continued until the temperature reaches 25°C. to yield a white, soft cream with a viscosity of about 8,000-12,000 cps. If it is desired to  
20           increase the viscosity of the resulting emulsion, shear can be applied using a conventional homogenizer, for example a Silverson L4R homogenizer with a square hole high shear screen. Normally, this step is not  
25           required since the viscosity of the emulsion can increase during dissolution of the active agent.

          The topical composition of the present invention is made by blending about 1 to 20 parts by weight, preferably 5 to 15 parts, of  
30           the hair-growth-inhibiting active agent, preferably DFMO, with correspondingly 99 to 80 parts by weight, preferably 95 to 85 parts, of the vehicle prepared as described above, and adjusting the pH to about 3.5 with aqueous  
35           sodium hydroxide (10%) or hydrochloric acid (10%). Of course, the topical composition could also be fabricated by including the active agent



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in the water phase during the aforescribed vehicle preparation.

#### EXAMPLE

Two vehicles were prepared having the composition designated Ex. I and Ex. II in the above Table according to the aforescribed procedure. The two vehicles contained 0.83 and 0.55 parts Phenonip respectively. To four separate batches of each vehicle was then added with mixing sufficient DFMO to produce topical compositions containing 2.5, 5, 10 and 15% DFMO. Thus, a total of eight topical compositions were prepared in all. Each composition was tested for hair growth inhibition using a standard hamster flank organ hair mass study as described in the previously identified four U.S. patents. For comparison, a control composition containing vehicle only was tested (IV and II-V below), as well as a composition containing 10% DFMO in the water-ethanol vehicle shown in Ex. I of U.S. 5,096,911 (W-E below). The results of these studies were as follows:

	<u>Com- position</u>	<u>% Inhibi- tion</u>	<u>Com- position</u>	<u>% Inhibi- tion</u>
25	I-A (15% DFMO)	84.2	II-A (15% DFMO)	89.1
	I-B (10% DFMO)	87.6	II-B (10% DFMO)	91.4
	I-C (5% DFMO)	84.5	II-C (5% DFMO)	85.5
	I-D (2.5% DFMO)	60.0	II-D (2.5% DFMO)	81.4
	I-V (0% DFMO)	-	II-V (0% DFMO)	-
30	W-E (10% DFMO)	68.3	W-E (10% DFMO)	72.6

As can be seen, each of the compositions of the invention, namely I-A through I-D and II-A through II-D, were highly efficacious in inhibiting mammalian hair growth. Similarly, beard hair growth inhibition is obtained when such compositions are applied to the human face. Remarkably, the above data also

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demonstrate that the present compositions are superior in efficacy to a water-ethanol composition which contains penetration enhancers. This suggests that the present  
5 composition achieves either enhanced skin penetration of the active agent or increased residence time of the active agent at the treated site. Moreover, the compositions of the invention remain stable over an extended period  
10 of time and have aesthetically pleasing attributes.

The topical compositions of the present invention are applied to mammalian skin, particularly the human face, on a daily or twice  
15 daily basis to provide a level of active agent of about 10 to 2000 micrograms per square centimeter of skin. Obviously, the application dose may be varied to achieve a suitable level of effectiveness for each individual being  
20 treated.

It will be apparent that equivalent materials may be substituted for those specified in the aforementioned table of ingredients without departing from the spirit and scope of  
25 this invention. For example, other water-soluble, pharmacological agents may be delivered to the skin by incorporating from about 1 to 20% of such an agent in the previously described vehicle.

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C L A I M S

1. A topical composition for inhibiting mammalian hair growth which comprises about 1 to 20 parts by weight of a water-soluble, hair-growth-inhibiting active agent dispersed in about 99 to 80 parts by weight correspondingly of a vehicle comprising an oil-in-water emulsion of the following components in parts by weight:

	Water	78 to 87
10	Glyceryl Stearate SE	2.8 to 4.8
	PEG-100 Stearate	2.7 to 4.7
	Cetearyl Alcohol	1.9 to 3.3
	Ceteareth-20	1.6 to 2.7
	Mineral Oil	1.7 to 2.7
15	Stearyl Alcohol	1.0 to 2.0
	Dimethicone	0.3 to 1.0

2. The composition of claim 1, adjusted to a pH of about 3.5 and optionally comprising a pH buffer.

- 20 3. The composition of claim 2, comprising 5 to 15 parts by weight of said active agent dispersed in 95 to 85 parts by weight correspondingly of said vehicle.

4. The composition of claim 3, wherein  
25 said vehicle comprises an oil-in-water emulsion of the following components in parts by weight:

	Water	80.84
	Glyceryl Stearate SE	4.24
	PEG-100 Stearate	4.09
30	Cetearyl Alcohol	3.05
	Ceteareth-20	2.50
	Mineral Oil	2.22
	Stearyl Alcohol	1.67
	Dimethicone	0.56

- 35 5. The composition of claim 3, wherein said vehicle comprises an oil-in-water emulsion of the following components in parts by weight:

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	Water	85.53
	Glyceryl Stearate SE	2.97
	PEG-100 Stearate	2.86
	Cetearyl Alcohol	2.14
5	Ceteareth-20	1.75
	Mineral Oil	2.22
	Stearyl Alcohol	1.17
	Dimethicone	0.56
	Citric Acid	0.25
10	6.	The composition of claim 1, 2, 3, 4, or 5, wherein said active agent is 2-(difluoromethyl)-2,5-diaminopentanoic acid.
15	7.	A method of inhibiting mammalian hair growth which comprises applying to the skin of a mammal an effective amount of a topical composition according to claim 1, 2, 3, 4, or 5.
	8.	The method of claim 7, wherein the active agent in said topical composition is 2-(difluoromethyl)-2,5-diaminopentanoic acid.
20	9.	The method of claim 8, wherein said topical composition is applied daily or twice daily at a level sufficient to provide about 10 to about 2000 micrograms of active agent per square centimeter of skin.
25	10.	The method of claim 8, wherein said topical composition is applied to human skin.
30	11.	A topical composition for delivering a water-soluble, pharmacological agent to the skin which comprises about 1 to 20 parts by weight of said water-soluble, pharmacological agent dispersed in about 99 to 80 parts by weight correspondingly of a vehicle comprising an oil-

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in-water emulsion of the following components in parts by weight:

	Water	78 to 87
	Glyceryl Stearate SE	2.8 to 4.8
5	PEG-100 Stearate	2.7 to 4.7
	Cetearyl Alcohol	1.9 to 3.3
	Ceteareth-20	1.6 to 2.7
	Mineral Oil	1.7 to 2.7
	Stearyl Alcohol	1.0 to 2.0
10	Dimethicone	0.3 to 1.0

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 93/02684

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 A61K7/06; A61K7/155		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	WO,A,8 602 269 (HANDELMAN) 24 April 1986 cited in the application see page 10, line 1 - line 31; claims 1-10; example 1 -----	1-11
<p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p>		
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WO-A-8602269	24-04-86	US-A- 4720489	19-01-88
		AU-B- 590730	16-11-89
		AU-A- 4867385	02-05-86
		CA-A- 1262335	17-10-89
		DE-A- 3585526	09-04-92
		EP-A, B 0198893	29-10-86
		JP-T- 62500932	16-04-87
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